

**REMARKS/ARUGMENTS**

Upon entry of this amendment, claims 1, 3 and 26-28 will be amended and claims 29-34 will be added, whereby claims 1-34 will be pending. Claims 1, 10 and 16 are independent claims.

Claim 1 is amended here in the manner indicated in the response to the rejection based upon Tagawa. Claim 3 is amended to correct a typographical error. Still further, claims 26-28 have been amended to even be more in conformance with standard U.S. practice, and no estoppel should be deemed to be raised by what should be considered to be cosmetic changes. Moreover, claims 29-34 have been added which are similar to claims 26-28, but dependent upon independent claims 10 and 16.

Reconsideration and allowance of the application are respectfully requested.

**Discussion Of Interview**

Applicants express appreciation for the courtesies extended by the Examiner to Applicants' representative Arnold Turk at a December 11, 2003 personal interview at the Patent and Trademark Office.

During the interview, Applicants' invention as disclosed and claimed in the application was discussed with the Examiner.

Moreover, Applicants discussed with the Examiner that the Japanese document discussed beginning at page 1, second full paragraph, under the "Background Art" section of Applicants' specification is a family member of Tagawa utilized in the rejection of record.

Moreover, Applicants indicated that there is a miscalculation error at page 2, line 19 of Applicants' specification.

Still further, Applicants pointed out support for amendment of claim 1 to recite "10 to 40 mole%".

The Examiner indicated that he would consider Applicants' arguments, and requested an English translation of the Japanese document.

Arguments as presented during the interview, and further arguments based upon a further review of the application are included herein.

#### **Consideration Of Disclosure Statements**

Applicants express appreciation for the acknowledgment on the record of Applicants' disclosure statements filed January 25, 2002, March 4, 2002 and August 22, 2002, whereby the record reflects the Examiner's consideration of these disclosure statements.

Moreover, Applicants express appreciation for the attachment of initialed copies of the Forms PTO-1449 submitted with the disclosure statements filed March 4, 2002 and August 22, 2002, whereby the documents cited thereon will appear on the face of the issued patent.

Moreover, Applicants note that the Office Action indicates that the Forms PTO-1449 submitted with the January 25, 2002 disclosure statement are not present in the file. Therefore, Applicants are submitting additional copies of these forms accompanied by a date-stamped mailroom receipt evidencing the filing of these papers on January 25, 2002. Applicants therefore respectfully request that the Examiner initial these forms, and to include an initialed copy of these forms with the next communication from the Patent and Trademark Office. Of course, if any additional documents are needed to complete the record, the Examiner is respectfully requested to

contact the undersigned to discuss the same. Moreover, if any fees are required, authorization is provided herein to charge any required fee to Deposit Account No. 19-0089.

**Therefore, Applicants respectfully request that the Examiner initial the Forms PTO-1449 submitted herewith to even more clearly confirm consideration of the previously submitted information, and to ensure the listing of the cited documents on the face of the issued patent.**

#### **Claim Of Priority**

Applicants note that this application claims priority of Japanese Application Nos. 11-115737, filed April 23, 1999, and 11-115738, filed April 23, 1999. In this regard, a copy of the Form PCT/IB/304 was submitted with the papers when entering the national stage. The Examiner is therefore respectfully requested to acknowledge the claim of foreign priority in the next communication from the Patent and Trademark Office as well as receipt of the certified copies of the priority documents in this national stage application.

#### **Formal Drawings**

Applicants note that the Office Action does not object to the drawings filed when Applicants entered the national stage. Therefore, Applicants assume that the drawings submitted when entering the national stage are acceptable, and that no further action is required by Applicants.

**Response To Rejection Under 35U.S.C. 112, Second Paragraph**

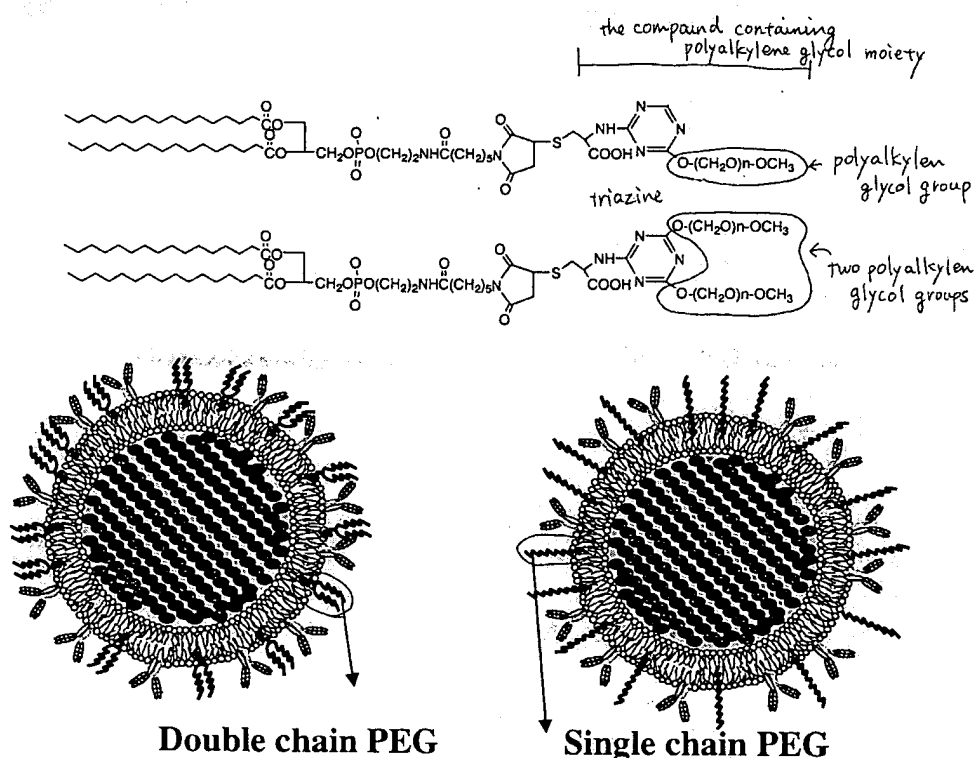
Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the rejection asserts that that clarification is requested as to what is included by “compound containing a polyalkylene glycol moiety”, because the rejection asserts that a careful review of the specification indicates the use of polyalkylene glycol as such and not a compound having a polyalkylene glycol. The rejection also questions “compound has two polyethylene glycol groups” recited in claims 6 and 20.

In response, Applicants respectfully submit that one having ordinary skill in the art would readily understand the metes and bounds of Applicants claims.

Thus, one having ordinary skill in the art would readily understand that the terminology "compound containing a polyalkylene glycol moiety" has the same meaning as the definition of a "compound containing a polyalkylene glycol" as explained in Applicants' specification, at lines 10 to 26. The terminology "compound containing a polyalkylene glycol" means, for example, a compound having a polyethylene glycol group wherein the polyethylene glycol group is attached to a triazine derivative or to a thiolated compound as explained in Applicants' specification at page 8, lines 21 to 23. Moreover, it is disclosed in Applicants' specification, at page 8, lines 10-11, that, “When polyethylene glycol is used, those having a molecular weight of about 2,000 to 7,000 Da, preferably about 5,000 Da, can be used.” Still further, it is disclosed in Applicants' specification, such as at page 8, line 22, that, “The compound may have two polyalkylene glycol groups (two-chain type).”

Still further, Applicants draw the Examiner's attention, for example, to U.S. Patent No. 5,264,221 which is a family member of JP 4-346918, which is utilized in the rejection of record, wherein similar terminology is utilized.

Below Applicants submit herewith examples of compounds containing polyalkylene glycol moieties, including a single polyalkylene glycol group and two polyalkylene glycol groups.



Accordingly, the rejection is without appropriate basis, and should be withdrawn.

However, as discussed with the Examiner at the above-noted interview, if the Examiner deems that it would be beneficial to amend the claims to even further clarify their language, the Examiner is respectfully requested to contact the undersigned to discuss the same.

**Response To Rejections Based Upon Prior Art**

In response to the rejection of claims 1-28 under 35 U.S.C. 102(b) as being anticipated by Tagawa, U.S. Patent No. 5,264,221, Applicants respectfully submit the following.

Initially, as discussed with the Examiner during the above-noted interview, Applicants' specification, beginning at page 1, "Background Art" section, beginning in the second paragraph, discusses and contrasts Japanese Patent Unexamined Publication (Kokai) No. 4-346918 (hereinafter "JP '918") with the invention that is disclosed and claimed in the instant application. Tagawa is a family member of JP '918, and this family relationship between Tagawa and JP '918 is set forth in the Information Disclosure Statement, filed January 25, 2002. Despite the family relationship that has been presented on the record, the rejection neither indicates such relationship, nor does the rejection address any of the discussion of JP '918 in Applicants' specification.

Still further, it is noted that Tagawa includes overlapping inventors with the present application, in that the inventors named in Tagawa include, amongst other co-inventors, Toshiaki Tagawa and Saiko Hosokawa, who are the inventors of the presently claimed invention. Accordingly, Applicants have, by the present invention, provided improvements over prior art of which they were co-inventors.

Still further, as discussed with the Examiner during the above-noted interview, an error appears in Applicants' specification, as originally filed, wherein at page 2, line 19 (first full paragraph, line 6 thereof), " 1.7 mole%" should, in fact, be ---3.3 mole%---. Applicants have therefore amended the specification to avoid this error in the present amendment.

As discussed with the Examiner during the above-noted interview and as noted above, JP '918 corresponds to Tagawa, which is being utilized in the present rejection. The Examples of JP '918 include the same Examples 1 to 3 of Tagawa.

Applicants note that Tagawa discloses the use of a thiolated antibody in a ratio of 0.1 mol% to 20 mol% based on 1 mol of maleimide group (column 4, lines 9 to 7 from the bottom). Also, Tagawa discloses in Example 3, a PEG modified liposome bound with an antibody.

As explained in Example 3 of Tagawa, the liposome disclosed in Example 3 was prepared according to the method described in Example 2, which means that 100 mg of lipid was used for preparation of the liposome of Example 3. According to the method for preparation of Example 2, maleimidated lipid is present at about  $3\mu\text{ mol}$  in total, and a half of the maleimidated lipid (about  $1.5\mu\text{ mol}$ ) is assumed to be present outside the liposome

Under the above assumption, 5 mg of the antibody Fab' (molecular weight 50000,  $0.1\mu\text{ mol}$ ) corresponds to 3.3 mole % based on 1 mol of the maleimidated lipid. Among  $5\mu\text{ mol}$  PEG used,  $1.4\mu\text{ mol}$  ( $1.5$  minus  $0.1\mu\text{ mol}$ ) of PEG is bound to the liposome by means of the maleimide group, which corresponds to 47 mol % based on 1 mole of the maleimidated lipid.

Thus, an amount of the antibody bound to the disclosed liposome in Example 3 of JP '918 can be calculated to be 3.3% mol (theoretical value) based upon one mole of maleimidated lipid, because Fab' antibody having a molecular weight of 50,000 was used in the experiment. This value of 3.3% mol is not explicitly disclosed in Example 3 or any other portion of JP '918 (or Tagawa), but is present therein in view of an antibody molecular weight of 50,000.

However, during preparation of the specification for filing the PCT application, the

inventor erroneously calculated the amount of the bound antibody in Example 3 of JP '918 as "1.7 mol%", because he misunderstood at that time that the antibody used in Example 3 was F(ab')<sub>2</sub> having a molecular weight of 100,000 instead of 50,000. Thus, the specification of the present application based on the PCT application contained the erroneous value of "1.7 mol%" at page 2, line 19. The result of the erroneous calculation was not included in the basic Japanese patent applications, i.e., Japanese Application Nos. 11-115737 and 11-115738, on which the priorities for the PCT application are claimed.

During the above-noted interview, the Examiner discussed the submission of a translation of JP '918 for supporting the change to the specification. However, as noted above, the mol% indicated in Applicants' specification for JP '918 is not explicitly disclosed therein. The miscalculation was erroneously indicated in the present application based upon a miscalculation based upon the erroneous use of 100,000 as the molecular weight of the antibody instead of the correct molecular weight of 50,000.

Accordingly, the correction of the specification is being made herein to more accurately provide an indication of the disclosure of the Tagawa, which is by overlapping inventors with the present application, in accordance with its disclosure. Thus, Applicants are removing incorrect disclosure from their specification. In any event, Applicants are clarifying the record that they are not in any manner making any admission that JP '918 discloses or can be considered to disclosed "1.7 mole%", and that this value should more accurately be ---3.3 mole%---

Still further, as discussed with the Examiner at the above-noted interview, claim 1 is amended herein to recite an amount of the bonded compound is 15 to 40 mole% based on one mole



of the maleimidated lipid contained in the liposome. This amendment avoids the amount which, as noted above, would be included in Tagawa. As discussed with the Examiner, support for this amendment appears in Applicants' originally filed specification, such as at page 14, line 12, wherein an upper limit of about 40 mole% based on one mole of maleimidated lipids is disclosed

Applicants respectfully submit that Tagawa does not teach each and every element as recited in Applicants' claims whereby the anticipation rejection is without appropriate basis. Thus, Tagawa does not teach each and every element recited in Applicants' independent claim 1, which is directed to a liposome wherein a compound containing a polyalkylene glycol moiety is bonded through a thioether group to a liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 40 mole% based on one mole of the maleimidated lipid contained in the liposome.

Still further, Applicants respectfully submit that Tagawa does not teach each and every element recited in Applicants' independent claim 10, which is directed to a liposome wherein an antibody is bonded through a thioether group to a liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded antibody is 0.1 to 2 mole% based on one mole of the maleimidated lipids contained in the liposome.

Still further, Tagawa does not teach each and every element recited in Applicants' independent claim 16, which is directed to a liposome wherein a compound containing a polyalkylene glycol moiety and an antibody are bonded through thioether groups to a liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of

the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 0.4 to 0.7 mole% based on one mole of the maleimidated lipids contained in the liposome.

Moreover, Applicants respectfully submit that Applicants' dependent claims further patentably define Applicants' invention for the elements further included therein.

For example, amongst other features recited in Applicants' claims which are not taught in Tagawa, Applicants claims include, as recited in independent claim 1, an amount of the bonded compound is 15 to 40 mole% based on one mole of the maleimidated lipid contained in the liposome; as recited in independent claim 10, an amount of the bonded antibody is 0.1 to 2 mole% based on one mole of the maleimidated lipids contained in the liposome; and as recited in claim 16, an amount of the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 0.4 to 0.7 mole% based on one mole of the maleimidated lipids contained in the liposome.

In view of the above, the anticipation rejection should be withdrawn.

### CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

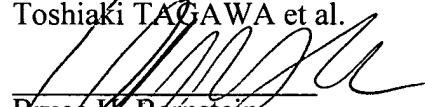
Applicant therefore respectfully requests that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

P21620.A08

Application No. 09/926,358

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
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*Rps. 33,094*

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